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Value of the prognostic nutritional index after liver transplantation of hepatocellular carcinoma patients

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is an important cause of cancer-related deaths in the world. Liver transplantation (LT) is a major treatment option for HCC. Therefore, studies predicting the prognosis of patients after transplantation have special importance.

Materials and Methods: Three hundred and ninety-six patients who underwent LT for HCC between March 2006 and November 2021 were enrolled in this study. The prognostic nutritional index (PNI) was analyzed to evaluate its use in the prognosis of patients after LT. Receiver operating curve (ROC) analysis was performed to detect the cutoff values and then logistic regression and survival analyses were performed to identify independent risk factors of prognosis.

Results: Overall survival (OS) was 9 years (8.2–9.7), disease-free survival (DFS) was 8.7 years (7.9–9.4) and recurrence was 19%. The median PNI value was 35 (15.7–116). Child–Pugh score-A was significant for DFS (P = 0.042) with a cutoff value of 31.02 in ROC analysis. However, no correlation was found between PNI and either OS, DFS, or recurrence.

Conclusion: Pre-operative PNI level may not be a good indicator for predicting the survival or recurrence of HCC patients with LT. Further prospective studies are needed to evaluate the importance of PNI levels in patients with LT for HCC.

Keywords: Hepatocellular cancer, Live donor, Prognostic nutritional index

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and is the third most common cause of cancer-related deaths. Unlike other solid malignancies, most HCC develops particularly on the basis of chronic liver disease associated with liver cirrhosis due to viral hepatitis or ethanol consumption. Despite remarkable developments in early diagnosis, sufficient surgery, adjuvant chemotherapy, and liver transplantation (LT), HCC patients have high rates of recurrence or metastasis within 5 years of treatment. Therefore, many ongoing studies are present to assess the early progression of the disease and to improve

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the survival of patients.[1] Immune nutritional status has been shown to be associated with prognosis in various malignancies, and the inflammatory response promotes tumor growth, invasion, angiogenesis, and metastasis.[2,3] The prognostic nutritional index (PNI), based on the concentration of albumin in peripheral blood and the number of lymphocytes, is largely affected by the nutritional status of the patients' and since cancer patients are often malnourished, PNI is often used to predict the prognosis.[4] In a meta-analysis, the prognostic value of PNI has been studied in different types of cancer.[5] This meta-analysis includes 14 studies involving 3413 cancer patients, and it was found that PNI affects overall survival (OS), and post-operative complications but not with cancer-specific survival. In meta-analysis and studies specific to different cancer types, PNI was determined as a prognostic factor.[6-8] These results show that low PNI is the risk factor for a poor prognosis in cancer patients.

There are many studies investigating the prognostic value of PNI in HCC patients who undergone liver resections.[9-12] However, studies that analyzed the prognostic value of PNI in HCC patients after LT contain few and limited data.[13,14]

In this study, we aimed to analyze the prognostic value of PNI after LT in HCC patients.

Materials and Methods

This study has Ethic Committee approval by Inonu University University Scientific Research and Publication Ethics Committee (Approval date and number: December 13, 2022, and 2022/4204).

Patients who underwent LT due to HCC between March 2006 and November 2021 were included in the study. Those with post-transplant follow-up period <3 months were excluded from the study. Total 396 cases were included in the study. Data were retrospectively analyzed through structured and prospectively collected databank.

PNI was calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3). PNI levels were compared with age (mean, PNI levels above and below the age of 55), Ethology (viral, cryptogenic, and other), sex, largest tumor size (≤5 cm, >5 cm), venous invasion, body mass index (BMI), alpha-fetoprotein levels (AFP) (≤200, >200), and tumor differentiation were analyzed. Inclusion criteria such as Milan, Malatya, and Expanded Malatya were recorded.[15-17] A number of nodules, Meld score, Child–Pugh score, and liver function tests were also noted. All pre-operative cases underwent with physical examination, routine blood tests, and thoracoabdominal tomography (CT). After 3 months following the operation, routine blood tests and AFP levels were checked quarterly a year. CT, ultrasonography, or magnetic resonance imaging were performed 3 times a year.

Statistical Analysis

All statistical analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Continuous and categorical variables were analyzed with Mann – Whitney U-test. The chi-square test was used to compare the categorical values. In a comparison of more than two independent groups, ANOVA and Kruskal–Wallis tests were used according to normality analysis. Cox regression was used to calculate disease-free survival (DFS) and OS. Survival analysis of categorized data was analyzed with Kaplan–Meier.

Results

Three hundred and ninety-six patients with a median age of 56 (2–72), 86% of males and 14% of females were included in the study. The general demographic data of the patients are shown in Table 1. OS was 9 years (8.2–9.7),

Table 1. Demographic characteristics of patients

	Median (Min–Max)
AFP	12.8 (0.2–20179)
MTD, cm	3.00 (0.1–24)
Number of nodules	2 (01–36)
BMI	25.8 (16.3–46.9)
Total bilirubin	1.84 (0.2–20179)
AST	59.00 (9–7789)
ALT	43.00 (10–3535)
ALP	119.5 (28–2327)
GGT	70.5 (11–1396)
Albumin	2.9 (1.2–5.2)
PNI	35 (15.7–116)
Creatinine	0.78 (0.37–13.8)
INR	1.32 (0.8–4.1)
Hb	12.8 (6.3–739)
Htc	37.8 (19–58)

AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: Gamma-glutamyl transferase; Hb: Hemoglobin; Htc: Hematocrit; MTD: Maximum tumor diameter; INR: International Normalized Ratio; PNI: Prognostic nutritional index.

DFS was 8.7 years (7.9–9.4), and recurrence was 19%. The median PNI value was 35 (15.7–116). First, cox regression analysis was performed to determine the correlation between PNI and OS, and DFS. There was no correlation between PNI, OS, DFS, or recurrence (p=0.622; p=0.539; and p=0.548, respectively). Receiver operating curve (ROC) analysis could not reveal a significant cutoff value. Factors that may be associated with PNI were checked in subgroup analyses. PNI values between the groups were compared. Significant differences were found in BMI, etiology, AFP levels ≤200, number of nodules more than one, MELD score ≤14, and Child–Pugh score (Table 2). In subgroup survival analysis of PNI revealed that "Child–Pugh score A" was significant in DFS (p=0.042) with a cutoff value of 31.02 in ROC analysis (Fig. 1). The correlation between PNI and continuous variables that could not be categorized was also analyzed. A negative correlation was detected with PNI INR, total bilirubin, AST, and ALP (p<0.001) (Table 3).

Discussion

The number of lymphocytes in the systemic circulation reflects the host cytotoxic immune response to HCC. The serum albumin level is the parameter that best reflects the systemic nutritional status and is the determining factor in immune reactions against cancer cells. Therefore, PNI may reflect the prognosis of patients with HCC more precisely than other inflammatory and nutritional indicators.

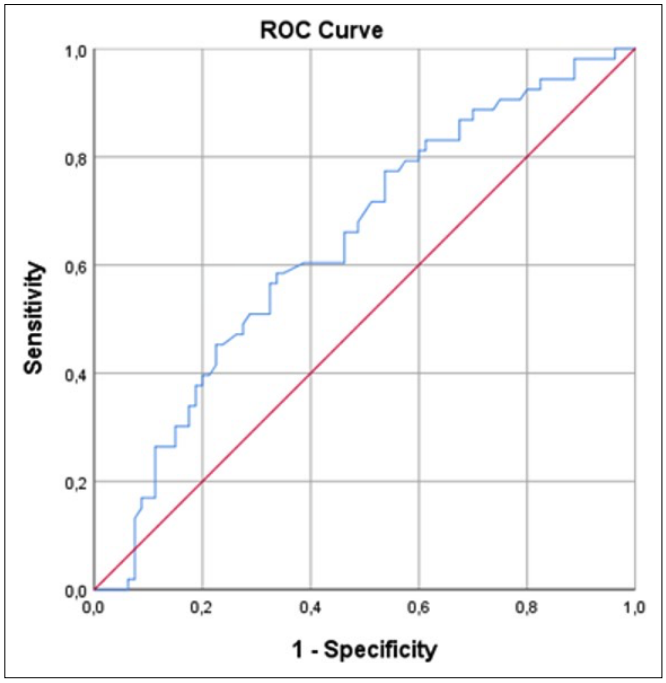

Figure 1. ROC analysis of PNI and DFS for Child A patients.

[12] There are many studies on PNI on predicting the survival and recurrence of HCC patients after resection. In a meta-analysis carried out by Man et al., low levels of PNI were related to recurrence, OS, and DFS. In this meta-analysis, it was found that PNI affects OS 1.8 times, DFS 1.4 times, and recurrence 1.92 times. ([OS [HR = 1.82, 95%CI: 1.44–2.31] and DFS [HR = 1.49], 95% CI: 1.06–2.07), recurrence (OR = 1.92, 95% CI: 1.33–2.76)].[18] In different HCC studies and meta-analysis, the PNI after hepatic resection was determined as a risk factor for both recurrence and survival.[9,11]

There are very few studies have evaluated the relationship between PNI and LT for HCC. Harimoto et al. could not find a correlation between PNI and prognosis of LT patients. In this study, the cutoff value for PNI was found 39.75 in ROC analysis; however, it was not significant.[19] The only comprehensive study that explored the relationship between PNI and HCC post-LT was conducted by Pravisan et al. Three hundred and twenty-four HCC patients were followed in this study. PNI values were recorded before and after the operation and the relationship between PNI and recurrence, and survival was investigated. PNI levels were 38.6 before the operation and 45.6 at post-operative 1 year. Post-operative PNI levels increased significantly until 3 months from the early post-operative period. However, from post-operative, the 3 months to 1st-year slight increase was observed in PNI levels. Although there was no correlation between the PNI levels before the operation and both recurrence and survival it was significant for the post-operative 1-year PNI levels. In this study, PNI values on pre-operative and post-operative days 1, 3, 5, 7, and at months 3, 6, and 12 were studied for mortality and tumor recurrence. It was found that the PNI levels on day 7 and months 3, 6, and 12 were associated with mortality, but only PNI levels on post-operative 12 months were associated with recurrence. PNI levels on post-operative 12 months were determined to be an independent risk factor for overall survival.[13] In another study, in which post-recurrence survival of patients with LT for HCC, a lower PNI level was associated with survival. In that study, the cutoff level of PNI was 40, only the patients with recurrent disease were evaluated, and the change in the PNI was not mentioned.[14] In our study, many subgroups, including the cutoff values of PNI in the literature, were also analyzed; but no correlation was found between pre-operative PNI level and OS, DFS, and recurrence after LT of patients with HCC. However, in subgroup analysis, the PNI cutoff level of 31 – which was very low – was significant

Table 2. Comparison of groups with PNI

	Frequency (%)	PNI (median, min–max)	p
Age			
≤55	201 (50.8)	34.4 (17.8–78)	0.138
>55	195 (49.2)	35 (15.7–116)	
Sex			
Male	340 (85.9)	35.4 (15.7–78)	0.683
Female	56 (14.1)	36.8 (17.8–116)	
Tumor size			
≤5 cm	296 (75)	34.8 (15.7–116)	0.69
>5 cm	100 (25)	36.7 (17.8–53.5)	
Etiology			
Viral	316 (80)	35.7 (15.7–116)	0.048
Cryptogenic	50 (13)	32.9 (20.2–50.6)	
Other	30 (7)	38.1 (21.8–116)	
Venous invasion			
Yes	184 (46.5)	34.8 (20.2–78)	0.271
No	212 (53.5)	35.5 (15–7–116)	
BMI			
≤20	34 (8.6)	40.5 ((23.7–78)	0.013
>20. ≤30	297 (75)	34.6 (17.8–116)	
>30	65 (16.4)	34.8 (15.7–54.9)	
AFP			
≤200	320 (82)	34.7 (20.2–116)	0.026
>200	71 (18)	37.6 (15.7–63.9)	
Tumor differentiation			
Well	165 (41.7)	34.9 (20.2–69.6)	0.44
Moderate–poor	231 (58.3)	35 (15.7–116)	
Milan criteria			
Within	199 (50.3)	35 (21.7–116)	0.202
Beyond	197 (49.7)	34.5 (15.7–63.9)	
Malatya criteria			
Within	150 (37.9)	35.6 (21.8–78)	0.351
Beyond	246 (62.1)	34.5 (15.7–116)	
Expanded malatya criteria			
Within	126 (31.8)	34.9 (15.7–63.9)	0.554
Beyond	270 (68.2)	35 (21.7–116)	
Number of nodules			
≤1	197 (50)	36.5 (17.8–57.5)	0.020
>1	199 (50)	34.1 (15.7–116)	
MELD score			
≤14	243 (61.4)	37.9 (20.2–78)	<0.001
>14	153 (38.6)	31.2 (15.7–116)	
Child–pugh score			
A	134 (33.8)	43.2 (27.5–78)	<0.001
B	173 (43.7)	33.3 (17.8–116)	
C	89 (22.5)	30.1 (15.7–63.9)	

AFP: Alpha-fetoprotein; BMI: Body mass index; MELD: Model for end-stage liver disease; PNI: Prognostic nutritional index.

Table 3. Correlation of liver function tests with PNI

Variable	Correlation coefficient	Sig. (2-tailed)	Number
Spearman's rho			
INR	−0.484**	0.000	302
Total bilirubin	−0.439**	0.000	396
AST	−0.297**	0.000	394
ALT	−0.070	0.164	395
ALP	−0.211**	0.000	394
GGT	0.076	0.131	394

**Highly significant different; INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase.

for DFS in patients with Child A. In our study, the pre-operative PNI value was 35, which was compatible with the literature.

In the literature, factors such as Edmonson-Steiner grading and microvascular invasion were associated with PNI; however, there was no correlation with, pre-operative AFP level, MELD score, Child–Pugh score, number of tumors, and tumor diameter.[13] In our study, AFP level, Meld score, Child–Pugh score, and the tumor number of more than one were found to have affected the pre-operative PNI value.

There may be some reasons why PNI is associated with prognosis in many types of cancer and is not associated with the prognosis of patients undergoing LT due to HCC. Cancer patients often experience malnutrition and exhibit weight loss. However, in our series, there were only 8% of patients with a BMI below 20. Since the production of albumin, a component of PNI also occurs in the liver, it is expected that albumin production in a healthy liver will be normal after transplantation. In our study, a negative correlation was found between PNI level and liver cirrhosis and liver function tests. While the increase in liver enzymes was associated with liver failure, the negative correlation with PNI value was not associated with prognosis, which can be explained by the normalization of enzyme values in the healthy liver after transplantation. Moreover, in the study of Pravisan et al., it was mentioned that the post-operative PNI level increases rapidly.[13] In patients who undergo LT for HCC, a decrease in PNI after transplantation is associated with a poor prognosis.[13,14] This explains why PNI is associated with the prognosis of other cancers but not with the prognosis of HCC patients undergoing LT.

Limitations of the Study

It was a single-centered experience and a retrospective study, although the number of patients was very high. In addition, pre-operative and post-operative treatment regimens were not considered in this study.

Conclusion

Pre-operative PNI level is not associated with predicting the survival or recurrence of patients with LT for HCC. Further prospective studies are needed to evaluate the pre-operative and post-operative changes in PNI in patients with LT for HCC.

Disclosures

Ethichs Committee Approval: This study has Ethic Committee approval by Inonu University University Scientific Research and Publication Ethics Committee (Approval date and number: December 13, 2022, and 2022/4204).

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Conflict of Interest: None declared.

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